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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,970	10/09/2003	Christopher E. Walsh	035052/270239	7990

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EXAMINER

LI, QIAN JANICE

ART UNIT PAPER NUMBER

1633

DATE MAILED: 10/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/681,970	<b>Applicant(s)</b> WALSH ET AL.	
	<b>Examiner</b> Q. Janice Li, M.D.	<b>Art Unit</b> 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 09 October 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 October 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>10/9/03</u> . | 6) <input type="checkbox"/> Other: _____  |

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### **DETAILED ACTION**

Claim 1 is pending in the application and under current examination.

#### ***Priority***

This application claims the benefit of priority to US application 10/095,718, filed 3/12/2002, now abandoned; which is a continuation of US application 09/689,430, filed 10/12/00, now abandoned; which claims the benefit of priority from U.S. provisional application 60/158,780, filed 10/12/99.

However, as indicated in the Office action mailed April 10, 2003 in the parent application 10/095,718, the claimed subject matter was a new matter for the Application 10/095,718, and hence the priority date for the instantly claimed subject matter has been established as the filing date of this application, i.e. October 9, 2003.

The status of each application in the continuation chain should be updated.

#### ***Information Disclosure Statement***

The information disclosure statement (IDS) submitted on October 9, 2003, and applicant's intention to copy claim 1 of U.S. Patent No. 6,200,560 are acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Applicant is reminded of the statutory time limitation set forth in 35 U.S.C. 135 b (1) for copying a claim of an issued patent.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating hemophilia in a mammal by providing recombinant adeno-associated virus (rAAV) virions comprising a nucleotide sequence encoding a **B-domain-deleted** Factor VIII, and administering such via the portal vein, does not reasonably provide enablement for treating hemophilia in a mammal by providing rAAV virions encoding the full length Factor VIII and via any route of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art, and whether the guidance provided in the specification support

Art Unit: 1633

the full scope of the claim to enable one of skill in the art to practice the claimed invention.

Claim 1 is drawn to a method of treating hemophilia in a mammal, comprising providing recombinant AAV virions comprising a nucleotide sequence encoding Factor VIII operably linked to expression control elements and administering said virions to a mammal. Given the broadest reasonable interpretation in light of the specification, the term "Factor VIII" encompasses the full length, and the B-domain-deleted Factor VIII.

However, the specification as filed fails to provide sufficient support for the full scope of the claimed subject matter, and teaches away from what is now claimed. The entire specification of the instant application is dedicated to teach that by encoding a biologically active, *B-domain deleted* factor VIII, "*the present invention utilizes the many advantages of rAAV vectors, while overcoming the constraints imposed by the limited packaging capacity of the AAV capsid*" (Specification, page 3, line 30 to page 4, line 2). The specification, replete with teachings of the size constrain of an AAV, offers a solution to the constrain as using biological active derivatives of FVIII with a reduced size. Therefore, both the parent and instant applications teach away from expressing a full length FVIII in an AAV virion.

In view of the state of the art and levels of the skilled in the art, *Dong et al* (Hum Gene Ther 1996;7:2101-12, IDS/79) teach, "OUR STUDIES SHOWED THAT THE OPTIMAL SIZE OF AAV VECTOR IS BETWEEN 4.1 AND 4.9 KB. ALTHOUGH AAV CAN PACKAGE A VECTOR LARGER THAN ITS GENOME SIZE, UP TO 5.2 KB, THE PACKAGING EFFICIENCIES IN THIS LARGE SIZE RANGE WERE SHARPLY REDUCED" (abstract). *Gnatenko et al* (British J Haematol 1999;Jan;104:27-36,

Art Unit: 1633

IDS/84) teach that given the size restrictions of the AAV virus, the utilities of the AAV vector for FVIII delivery appeared to be problematic, but can be surmounted by the use of B-domain-deleted FVIII (left column, page 28). Obviously, it is well known in the art at and before the instant priority date that the size of the full length FVIII precludes its packaging into an AAV virion.

Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for the claimed invention. However, the instant specification, consistent with the prior art of record, teaches away from what is now claimed with regard to using a rAAV encoding a full-length FVIII. Although the instant specification provides teachings of using the B-domain-deleted FVIII in an AAV vector, it is not enabled for its full scope because the specification does not teach how to overcome the art-known hurdles, i.e. how to make packaging the full-length factor VIII in an AAV virion feasible and expressing such efficiently, and whether any significant gene expression, or any therapeutic effect could be achieved *in vivo*.

Given the broadest reasonable interpretation, claim 1 encompasses treating hemophilia by administering a rAAV to a subject in need by any means of injection. However, the specification fails to teach the targeting ability of rAAV, and whether it can reach liver cells in sufficient amount when administered in a site remote from the liver. The specification only illustrates injections via portal vein (e.g. examples 6 & 11).

In view of the state of the art, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired cells *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art.

Art Unit: 1633

For example, *Verma* (Sept. 1997, *Nature*, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of *Verma* indicate a resolution to vector targeting has not been achieved in the art (see entire article). *Crystal* (1995, *Science*, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "AMONG THE DESIGN HURDLES FOR ALL VECTORS ARE THE NEED TO INCREASE THE EFFICIENCY OF GENE TRANSFER, TO INCREASE TARGET SPECIFICITY AND TO ENABLE THE TRANSFERRED GENE TO BE REGULATED" (page 409). The specification fails to teach a targeting mechanism for AAV, and fails to teach how to overcome the art known hurdles, and thus fails to provide an enabling disclosure to support the full scope of the claims.

Therefore, in view of the knowledge of the skilled in the art, the teachings of the specification, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects

Art Unit: 1633

for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by *Couto et al* (US 6,200,560, IDS/19).

Claim 1 is drawn to a method of treating hemophilia in a mammal, comprising providing recombinant AAV virions comprising a nucleotide sequence encoding Factor VIII operably linked to expression control elements and administering said virions to a mammal.

*Couto et al* teach a method of treating hemophilia in a mammal, comprising providing recombinant AAV virions containing a nucleotide sequence encoding Factor VIII operably linked to expression control elements and administering said virions to a mammal, wherein the nucleotide sequence encodes the light chain or heavy chain of FVIII, respectively, and administering the virions together to a mammal (e.g. fig. 7, and claim 16). Thus, *Couto et al* anticipate the instant claims.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by *Couto et al* (US 6,221,349, IDS/20).

*Couto et al* teach a method of delivering recombinant AAV virions containing a nucleotide sequence encoding Factor VIII operably linked to expression control elements and administering said virions to a mammal, wherein the nucleotide sequence encodes the light chain or heavy chain of FVIII, respectively, and administering the virions together to a mammal (e.g. fig. 7, and claim 16). Thus, *Couto et al* anticipate the instant claims.

Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by *Scallan et al* (Blood. 2003 Dec 1;102(12):3919-26. Epub 2003 Jul 31).

*Scallan et al* teach a method of treating hemophilia using adeno-associated viral 2 (AAV2) vectors to deliver the heavy and light chains of factor VIII separately, in doing so, they have overcome the packaging limitations of AAV, and achieved phenotypic correction of hemophilia A in mice. AAV vectors were constructed that use a liver-specific promoter and the cDNA sequences of either the human or canine heavy and light chains of FVIII (Fig. I). After intraportal vein injection of these vectors in hemophilia-A mice, therapeutic levels of active FVIII were achieved in plasma in a dose-dependent manner. Accordingly, *Scallan et al* anticipate instant claims.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Connelly et al* (US 5,935,935, IDS/16), in view of *Snyder et al* (USP 6,936,243) and *Dong et al* (Hum Gene Ther 1996;7:2101-12, IDS/79).

Claim 1 is directed to a method of providing and administering to a mammal recombinant AAV virions comprising a nucleotide encoding FVIII including a B-domain deleted FVIII.

*Connelly et al* teach a method of treating hemophilia in a mammal, comprising providing recombinant adenoviral vector containing a nucleotide sequence encoding Factor VIII derivatives operably linked to expression control elements and administering said rAdv to a mammal (abstract, examples 13-17). The illustrative embodiment in example 5 is a B-domain deleted factor VIII (column 19). *Connelly et al* do not teach using a rAAV vector for FVIII expression.

*Snyder et al* supplemented *Connelly et al* by establishing that it is well known in the art the advantage of using AAV gene therapy vector as opposed to rAdv. *Snyder et al* teach delivering therapeutic endogenous or exogenous polypeptides into liver cells of a mammal using rAAV vectors. They teach that treating hemophilia B in a canine model using an adenoviral-mediated delivery of Factor IX is hampered by the immune response against the viral gene products (paragraph 0033), and using a rAAV could overcome the hurdle (e.g. paragraph 0034). They teach that the rAAV provided by the invention could express a polypeptide at therapeutic levels in the liver and the circulation, and no toxicity or liver pathology was associated with the rAAV administration (paragraph 0052). The illustrative embodiment is delivering Factor IX, not FVIII. However, they teach that the method could be used in the delivery of many other therapeutic factors, such as Factor VIII (paragraph 0101). *Snyder et al* do not particularly teach the packaging size of the rAAV.

*Dong et al* supplemented the teachings of *Connelly et al* in view of *Synder et al* by a showing of the knowledge of the skilled at the time concerning the packaging ability of rAAV. *Dong et al* teach that the total genome size of the AAV vector influences the efficiency of its packaging into AAV virions, the optimal vector length for packaging is between 4.1 and 4.9 kb, and although the AAV can package a vector larger than its genome size, from 2 to 5.2 kb, the packaging efficiencies would be sharply reduced in the large sized range (Summary).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Connelly et al*, by simply substituting a rAdv with a rAAV as taught by *Synder et al*, and altering the length of the coding polynucleotide to maintain the optimal packaging size for the AAV vector as taught by *Dong et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the method because it is known in the art that B-domain deleted FVIII acts as the functional equivalent of a full-length FVIII, and it is known in the art that a rAAV does not induce the undesirable immune response as does a rAdv, and thus a long-lasting FVIII expression could be obtained by using a rAAV. Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

### **Conclusion**

No claim is allowed.

Art Unit: 1633

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave T. Nguyen** can be reached on 571-272-0731. The fax numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

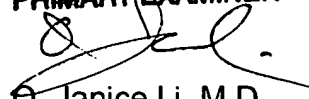
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Art Unit: 1633

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**Q. JANICE LI, M.D.**  
**PRIMARY EXAMINER**



Q. Janice Li, M.D.  
Primary Examiner  
Art Unit 1633

QJL  
September 29, 2005